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TREATMENT OF BACTERIAL ENDOCARDITIS*

The clinical diagnosis of bacterial endocarditis is simple when a patient exhibits fever, a heart murmur, enlargement of the spleen, clubbing of the fingers, embolic phenomena and other highly suggestive signs. It is more difficult when there is little to be found beyond an unexplained anemia, or manifestations of renal insufficiency with hematuria. Since the end result of treatment depends largely on the prompt institution of effective antimicrobial therapy, significant delay in diagnosis must be avoided. Prompt diagnosis can be achieved only by maintaining a high index of suspicion when faced with patients who have protracted fever with a heart murmur or other suggestive signs or symptoms.[1] Based on such clinical suspicion, diagnostic laboratory studies must be pursued. A statement concerning the etiologic organism is far more meaningful than separation of bacterial endocarditis into "acute" and "subacute." Treatment with antibiotics should never be started without a thorough attempt to recover the etiologic organism by culture. Rational antimicrobial therapy rests on the following concepts:

Principles of Therapy in Bacterial Endocarditis

Spontaneous recovery from bacterial endocarditis does not occur. Antibacterial defenses of the patient, which can control many other bacterial infections, are unable to eradicate the micro-organisms from their protected location within vegetations. Drugs which are predominantly bacteriostatic in therapeutic concentrations (e.g., sulfonamides, tetracyclines, chloramphenicol, erythromycin) generally do not cure bacterial endocarditis if employed alone.[2] Cure requires the administration of single or combined antibiotics which are capable of killing rapidly the etiologic micro-organisms. Suitable laboratory tests can often determine which drugs are most actively bactericidal.

The antibiotics must penetrate deeply into the organizing vegetations and achieve suitable concentrations at depths where bacteria proliferate or persist. The drugs must be administered for the protracted periods necessary to ensure that all organisms within the vegetation are nonviable and unable to proliferate when the drug is withdrawn.

For optimal therapy, the following steps are suggested:

1. Early suspicion of bacterial endocarditis, or diagnosis on clinical grounds.
2. Repeated attempts to culture the etiologic organism.
3. Laboratory tests to determine bactericidal drugs and concentrations.
4. Administration of such drugs in suitable concentration for a minimum of three to six weeks.
5. Follow-up by repeated clinical examinations and cultures for two months to detect possible relapse.
6. Assessment of ultimate damage resulting from infection or healing processes which may produce cardiac or renal failure after bacteriologic cure.

Contributions of the Laboratory

A. Isolation of the organism. For optimal therapy, the etiologic organism must be available for tests of its antibiotic sensitivity. In the majority of cases ultimately proved to be bacterial endocarditis, cultures of the blood are positive. In a small number of additional cases, the etiologic organism can be grown from bone marrow (iliac crest or sternum), and in 10-20 per cent of cases no positive cultures can be obtained. Among most patients who yield a positive culture, it can be obtained in the first three to five cultures drawn. Thus, it is rarely justified to take cultures and withhold therapy for more than one week. Treatment may have to begin without laboratory guidance and may later be modified as laboratory results become available. Conversely, it is only in exceptional cases that treatment may not be withheld for a few days, pending the collection of proper specimens for culture. The fear is often expressed that irreparable damage (e.g., rupture of a valve or a serious vascular accident) may occur during this delay. Such unfortunate accidents do happen, but there is no evidence that immediate adequate antimicrobial therapy could have prevented them. Following the administration of even small amounts of antibiotics, it is often difficult to obtain positive cultures. There-

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fore, in suspected bacterial endocarditis, antibiotics should never be given before blood cultures have been drawn. In probable cases of fulminating staphylococcal endocarditis, treatment should be started after two cultures have been secured in the first few hours of hospital stay.

B. Determination of antibiotic sensitivity. Although a significant number of cases of bacterial endocarditis (particularly those due to penicillin-sensitive *Streptococcus viridans*) can be effectively treated without the aid of laboratory tests, it must be recommended that organisms recovered from the blood (or bone marrow) should always be submitted to proper antibiotic sensitivity tests. The frequently employed tests for bacterial inhibition (e.g., disc tests) are meaningless and in this disease may be seriously misleading. Bacterial endocarditis is one of the few conditions where the physician must insist on laboratory tests which measure the bactericidal activity of drugs.[1-4] The tests should also give some quantitative information on the relative bactericidal power of different concentrations of single drugs and of drug combinations. Especially when dealing with relatively drug-resistant bacteria, it is essential that antibiotic combinations be tested. Relatively simple techniques for such tests have been described[4] and are available in many medical centers. Physicians in outlying areas may mail bacterial cultures to such centers to secure this important information. To avoid delay, treatment is generally started when the diagnosis is made and culture specimens have been secured, but the regimen is modified later according to the results of laboratory tests for bactericidal antibiotic action.

C. Estimation of antimicrobial drug levels in the blood stream. Reliable data are available indicating what average blood levels may be expected from different time-dose schedules of antibiotics. Thus it is rarely necessary to estimate blood levels in patients treated with well-established drugs. If it is desirable to ascertain that an effective concentration of the drugs used has been obtained, one need only take serum from the patient and establish that it is rapidly bactericidal *in vitro* for a culture of the patient's own bacterium.[5]

Choice of Antimicrobial Agents

Because of the seriousness of the disease, overtreatment in antibiotic dosage and length of therapy is generally desirable. Penicillin continues to be the single most effective and most important drug in bacterial endocarditis.[6] It is rapidly bactericidal for many streptococci, and in cases due to such organisms, administration of 2-5 million units of penicillin G daily for three to four weeks is generally curative. Ultra-short courses of treatment (10-20 days) often may be satisfactory, but are less reliable. Oral administration of penicillin is never advisable. The addition of streptomycin-dihydrostreptomycin (1-2 gm. daily, intramuscularly) enhances the bactericidal effect of penicillin against many gram-positive organisms. The combination of penicillin and streptomycin may also be employed to advantage against some alpha hemolytic streptococci. In infections due to enterococci (*Streptococcus faecalis*), this combination is often effective (usually 5-20 million units of penicillin, and 1-2 gm. of streptomycin-dihydrostreptomycin, daily for four to six weeks), while penicillin alone only suppresses that organism but does not eradicate it. Similar combinations are employed in cases diagnosed as bacterial endocarditis from which no organisms can be cultured.

In infections due to other organisms, no specific suggestions for therapy can be made but the results of laboratory tests must serve as a guide. In general, doses of drugs (often combinations) should be administered which are likely to produce blood and tissue levels several times higher than the concentrations necessary to kill the bacteria rapidly *in vitro*. With particularly resistant organisms, such as "hospital" staphylococci and gram-negative bacteria, more than two drugs are often used simultaneously to enhance the opportunity for mutual potentiation and to delay the emergence of drug-resistant variants. Here, too, laboratory guidance is helpful in the selection of drugs. With the more resistant organisms the tendency is to treat longer, up to eight weeks.*

Management

Rest and good nutrition probably speed recovery under antibiotic treatment and help regain normal cardiac function. Anticoagulants (e.g., heparin) contribute nothing and are no longer employed. Corticosteroids are probably contraindicated because of their tendency to enhance the spread of infection.

As soon as specimens for culture have been collected, a tentative antibiotic regimen is started. This is modified, if necessary, when laboratory results become available. Two or three days after beginning antimicrobial therapy and at weekly intervals thereafter, blood is obtained for culture to ascertain whether the organism originally present has been suppressed and to make sure that no other bacteria are present. A prerequisite for successful therapy is that these cultures become sterile, but this does not in itself guarantee a cure. Cultures are commonly negative during administration of antibiotics even if bacteria are only suppressed rather than eradicated. As soon as the drugs are discontinued, cultures may become positive again.

If the antibiotic regimen is effective, there is a marked improvement in the patient's well-being, and in most cases his temperature rapidly returns to normal. However, drug fever is not rare during successful treatment and embolic phenomena may continue for several weeks. These are disquieting events, but without compelling reasons the physician should not alter a regimen established on the basis of experience and laboratory findings.

*In some cases, treatment should be continued for more than eight weeks—Editor.

At the end of the agreed period of therapy, all antibiotics are discontinued and follow-up cultures are obtained at weekly intervals for two months. Continuing antibiotics beyond the period of full-scale therapy might "mask" a persisting infection and thus do harm. Continuing evaluation of cardiac function will permit early treatment of heart failure, should it occur as a result of myocardial damage, valvular injury, or fibrosis progressing after arrest of the infection.

In enterococcal and staphylococcal endocarditis, abscess formation in various tissues is not rare. These foci may have to be dealt with differently (e.g., surgical drainage) to avoid their reseeding the blood stream with bacteria.

Prophylaxis

Individuals with rheumatic or congenital heart disease and those recovered from bacterial endocarditis carry a known risk of acquiring bacterial endocarditis through the implantation of organisms during transitory bacteremia. In an effort to prevent such implantation, "prophylactic" antibiotics are often administered during episodes commonly associated with intense bacteremia, e.g., dental procedures, surgery on the upper respiratory or the urinary tract, and during respiratory infections. No proof exists that such prophylaxis is beneficial.[6] Nevertheless, it is recommended that persons who run a greater than ordinary risk receive antibiotics likely to affect the micro-organisms commonly entering the blood stream from the site manipulated. To deal with the commonest member of the respiratory flora, alpha hemolytic streptococci, 400,000 units of procaine penicillin G with 200,000 units of aqueous crystalline penicillin G may be injected an hour before and on each of two days following a dental procedure. Two million units of penicillin and 1 gm. of streptomycin daily might be injected on the day of, and for three days after, a urological procedure to avoid implantation of enterococci.

Failures of such "prophylaxis" do occur and therefore patients who run a greater than ordinary risk of acquiring bacterial endocarditis should be carefully followed.

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The opinions and conclusions expressed herein are those of the author and do not necessarily represent the official views of the Scientific Council of the American Heart Association.

Important Deadline . . .

ABSTRACTS OF PAPERS FOR 30TH ANNUAL SCIENTIFIC SESSIONS AMERICAN HEART ASSOCIATION

The 30th Annual Scientific Sessions of the American Heart Association will be held in Chicago, Illinois, on October 25 through 28, 1957, at the Association's Annual Meeting. Early submission of abstracts is advised; *the deadline is June 15, 1957.* Abstracts will be accepted only on forms which can be obtained from the Medical Director, American Heart Association, Inc., 44 East 23rd Street, New York 10, N. Y.

Papers intended for presentation should be based on original investigations in or related to the cardiovascular field. Abstracts must be submitted in triplicate, in a form suitable for publication in the Proceedings.

The Scientific Sessions again will feature a section for Scientific Exhibits. Requests for space and application forms also may be obtained from the Association's Medical Director. The deadline for these applications is June 15, 1957. All exhibit applications will be submitted for decision to the Program Committee of the Scientific Council.

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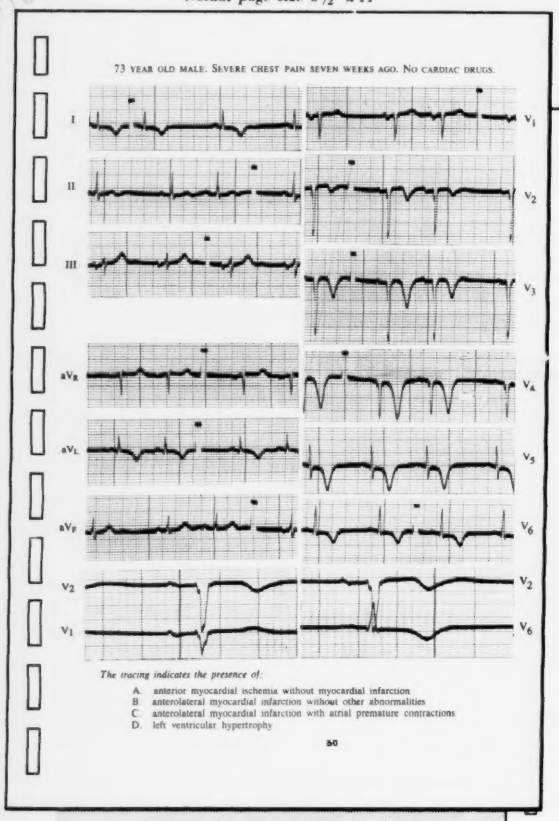


73 YEAR OLD MALE. SEVERE CHEST PAIN SEVEN WEEKS AGO. NO CARDIAC DRUGS.

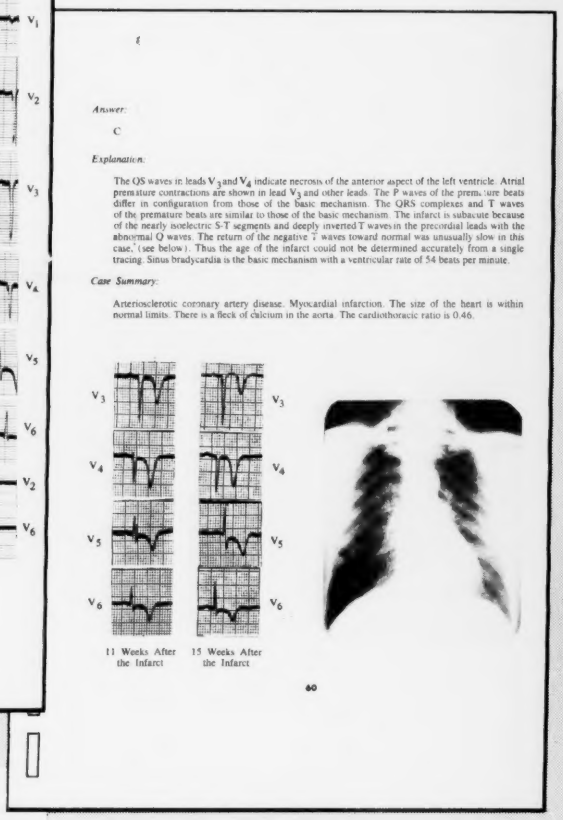
I, II, III, aVR, aVL, aVF, V2, V1, V1, V2, V3, V4, V5, V6, V2, V6

The tracing indicates the presence of:

A. anterior myocardial ischemia without myocardial infarction
B. anterolateral myocardial infarction without other abnormalities
C. anterolateral myocardial infarction with atrial premature contractions
D. left ventricular hypertrophy

50

Sample page, Volume I (Question Section)



Answer:

C

Explanation:

The QS waves in leads V_3 and V_4 indicate necrosis of the anterior aspect of the left ventricle. Atrial premature contractions are shown in lead V_3 and other leads. The P waves of the premature beats differ in configuration from those of the basic mechanism. The QRS complexes and T waves of the premature beats are similar to those of the basic mechanism. The infarct is subacute because of the nearly isoelectric S-T segments and deeply inverted T waves in the precordial leads with the abnormal Q waves. The return of the negative T waves toward normal was unusually slow in this case, (see below). Thus the age of the infarct could not be determined accurately from a single tracing. Sinus bradycardia is the basic mechanism with a ventricular rate of 54 beats per minute.

Case Summary:

Arteriosclerotic coronary artery disease. Myocardial infarction. The size of the heart is within normal limits. There is a fleck of calcium in the aorta. The cardiothoracic ratio is 0.46.

V3, V4, V5, V6, V3, V4, V5, V6

11 Weeks After the Infarct — 15 Weeks After the Infarct

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Sample page, Volume II (Answer Section)

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